**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the Application of

Dharmaraj Ramachandra RAO et al

Attn: Applications

Serial No.: To be assigned

Filed: June 17, 2005

For: A PROCESS FOR PREPARING DULOXETINE AND INTERMEDIATES FOR USE THEREIN

CONFIRMATION OF CLAIM FOR PRIORITY

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

The benefit of the filing date of the following prior foreign application filed in the following foreign country is hereby requested for the above-identified application and the priority provided in 35 USC 119 is hereby claimed:

Great Britain Application No. 0229583.0, filed December 19, 2002.

A copy of the priority document was filed in the International Stage (PCT).

It is requested that the file of this application be marked to indicate that the requirements of 35 USC 119 have been fulfilled and that the Patent and Trademark Office kindly acknowledge receipt of this document.

Respectfully submitted,

TPP/mat
Attorney Docket No.: TPP 31770

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Date: June 17, 2005

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

WAIN, Christopher, Paul
A.A. Thornton & Co.
325 High Holborn
London WC1V 7LE
United Kingdom

| | |
|---|---|
| Date of mailing (day/month/year)<br>09 February 2004 (09.02.2004) | |
| Applicant's or agent's file reference<br>CPW/20668 | **IMPORTANT NOTIFICATION** |
| International application No.<br>PCT/GB2003/005357 | International filing date (day/month/year)<br>10 December 2003 (10.12.2003) |
| International publication date (day/month/year)<br>Not yet published | Priority date (day/month/year)<br>19 December 2002 (19.12.2002) |
| Applicant<br>CIPLA LTD et al | |

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| Priority date | Priority application No. | Country or regional Office or PCT receiving Office | Date of receipt of priority document |
|---|---|---|---|
| 19 Dece 2002 (19.12.2002) | 0229583.0 | GB | 05 Febr 2004 (05.02.2004) |

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Signed P. Mahoney

Dated 9 January 2004

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*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

The Patent Office

Cardiff Road
Newport
South Wales
NP9 1RH

1. Your reference — CPW/20668

2. Patent application number *(The Patent Office will fill in this part)* — 0229583.0 — 19 DEC 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   Cipla Limited
   289 Bellasis Road
   Mumbai Central
   Mumbai 400 008
   India

   7789162001

   Patents ADP number *(if you know it)*

   If the applicant is a corporate body, give the country/state of its incorporation — An Indian Company

4. Title of the invention — A PROCESS FOR PREPARING DULOXETINE AND INTERMEDIATES FOR USE THEREIN

5. Name of your agent *(if you have one)* — A A THORNTON & CO

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — 235 HIGH HOLBORN
   LONDON WC1V 7LE

   Patents ADP number *(if you know it)* — 0000075001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|
| --- | --- | --- |

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | | Date of filing *(day / month / year)* |
|---|---|---|
| --- | --- | --- |

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

   *a) any applicant named in part 3 is not an inventor, or*
   *b) there is an inventor who is not named as an applicant, or*
   *c) any named applicant is a corporate body.*
   *See note (d))*

   YES

**Patents Form 1/77**

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| | |
|---|---|
| Continuation sheets of this form | |
| Description | 9 |
| Claim *(s)* | 6 |
| Abstract | 2 |
| Drawing *(s)* | - |

10. If you are also filing any of the following, state how many against each item.

| | |
|---|---|
| Priority documents | - |
| Translations of priority documents | - |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | - |
| Request for preliminary examination and search *(Patents Form 9/77)* | - |
| Request for substantive examination *(Patents Form 10/77)* | - |
| Any other documents *(please specify)* | - |

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 18.12.2002

12. Name and daytime telephone number of person to contact in the United Kingdom C P WAIN 01604 638242

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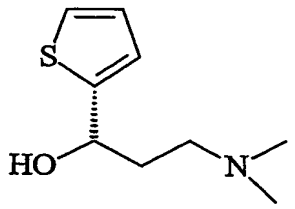
# A PROCESS FOR PREPARING DULOXETINE AND INTERMEDIATES FOR USE THEREIN

The present invention is concerned with a process for preparing duloxetine, in particular a process for preparing (+)duloxetine in enantiomerically pure form, and to intermediates for use therein.

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is a dual serotonin and norepinephrine reuptake inhibitor. (+)Duloxetine has particular therapeutic utility as an anti-depressant.

Duloxetine, and the preparation thereof, is described in US patents 5023269 and 4956388, and also Tetrahedron Letters, 31, (49), 7101-04, 1990. Seven different routes of synthesis have also been reported in Drugs of the Future 2000, 25(9) 907-916. These syntheses have involved either a resolution of a key intermediate or a stereospecific reduction of a keto group to the alcohol.

We have now observed that a particular chiral intermediate employed in the synthesis of (+)duloxetine, namely




undergoes considerable racemisation during coupling with a 1-naphthyl halide under the reaction conditions employed in the prior art. In particular, in the presence of a strong base, such as sodium hydride, and a protic polar solvent, such as DMSO, the dimesyl anion can be generated which can cause partial or complete racemisation of the condensed product.

There is, therefore, a need for an improved process for the preparation of (+)duloxetine which alleviates the problems associated with prior art processes as referred to above. We have developed such a process which is advantageous in obviating racemisation, so as to yield an enantiomerically pure form of (+)duloxetine. In particular, our process can be seen to achieve the above described advantage, by carrying out resolution as a final step in the reaction process (thereby obviating the opportunity for racemisation during preceeding intermediate process steps) and / or avoiding conditions that would result in the production of intermediate products that would be prone to racemisation.

According to the present invention, therefore, there is provided a process for preparing (+)duloxetine, or an acid addition salt thereof, which process comprises:

(i) resolving racemic (±)duloxetine with a chiral acid so as to obtain a salt of the chiral acid and (+)duloxetine, substantially free of (-)duloxetine; and

(ii) if desired, converting the salt prepared in step (i) to the free base or another acid addition salt as appropriate.

The resolution step (i) is achieved with a suitable chiral acid in a suitable solvent. The chiral acid can typically be selected from the group consisting of mandelic acid, tartaric acid, di-p-toluyl tartaric acid, dibenzoyl tartaric acid, camphor sulfonic acid and the like. Other suitable chiral acids may be determined by testing and the use thereof in a process as described above falls within the scope of the present invention. Preferably the chiral acid employed in a process according to the present invention is (-)di-p-toluyl tartaric acid. Suitably, the solvent employed is a lower alkanol, such as methanol or ethanol, although again other suitable solvents can be determined by testing and the use thereof in a process as described above falls within the scope of the present invention. A preferred solvent is methanol.

The salts of (+)duloxetine prepared by resolution step (i) represent a further aspect of the present invention and there is further provided by the present invention, therefore, a salt of a chiral acid and (+)duloxetine, substantially free of (-)duloxetine. Such salts of a chiral acid

and (+)duloxetine, substantially free of (-)duloxetine, are useful as intermediates for preparing the free base or another acid addition salt as appropriate.

Suitable salts provided by the present invention include (+)duloxetine mandelate, (+)duloxetine tartrate, (+)duloxetine di-p-toluyl tartrate, (+)duloxetine dibenzoyl tartrate, (+)duloxetine camphor sulfonate and the like. A preferred salt according to the present invention is (+)duloxetine di-p-toluyl tartrate, which is useful as an intermediate for preparing the free base or another acid addition salt as appropriate.

Intermediate salts prepared according to the present invention as described above can be converted to the free base or another acid addition salt according to step (ii) of a process according to the present invention. Suitably, an intermediate salt of the chiral acid and (+)duloxetine can be treated with a base, such as sodium hydroxide, to yield the free base. The free base itself can, if desired, be converted into an acid addition salt thereof.

Suitable acid addition salts which may be formed in step (ii) include those formed with pharmaceutically acceptable organic or inorganic acids and are well known to those of skill in the art. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephathalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonates, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts. Preferred pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic

acids such as oxalic acid and maleic acid. A particularly preferred acid addition salt is the hydrochloride.

A particularly preferred process according to the present invention comprises:

(i) resolving racemic (±)duloxetine with di-p-toluyl tartaric acid so as to obtain (+)duloxetine di-p-toluyl tartrate, substantially free of (-)duloxetine; and

(ii) converting (+)duloxetine di-p-toluyl tartrate prepared in step (i) to (+)duloxetine hydrochloride.

A process according to the present invention preferably yields (+)duloxetine in substantially pure enantiomeric form. Thus the ratio of (+)duloxetine: (-)duloxetine as prepared by the present invention may be at least about 94:6, such as at least about 98:2, or more preferably at least about 99:1. Preferably (+)duloxetine prepared by a process according to the present invention has an enantiomeric purity of at least about 99%, or more particularly at least about 99.5%.

The proportion of (+)duloxetine achieved by a process according to the present invention can be increased by effecting one or more, for example two or three, recrystallisations in step (i). To this end, a crystalline salt obtained as a result of resolution may be dissolved in a solvent therefor and the salt recrystallised from the resulting solution. In this way the proportion of a salt with (+)duloxetine can thus be increased until it is substantially pure, that is substantially only a salt with (+)duloxetine is present.

The mother liquor from resolution step (i), or the mother liquor from the or each recrystallisation step, is enriched with (-)duloxetine. (-)Duloxetine present in one or more of these liquors, or the pooled liquors, may be converted into (±)duloxetine for reuse in a process according to the present invention substantially as hereinbefore described.

A further preferred aspect of a process according to the present invention comprises:

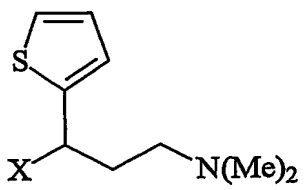
(i) resolving racemic (±)duloxetine with a chiral acid and obtaining a mother liquor enriched in (-)duloxetine;

(ii) converting (-)duloxetine obtained from step (i) to (±)duloxetine; and

(iii) if desired, employing (±)duloxetine obtained from step (ii) in a process according to the present invention substantially as hereinbefore described.

Suitably, one or more mother liquors obtained from a process as described above, or pooled such mother liquors, may be treated with a base to remove any residual chiral acid and to thereby afford the free base enriched in (-)duloxetine. The free base can then be converted to the racemate, typically by reflux in a suitable solvent for several hours, optionally in the presence of a suitable acid (e.g. HCl) or a base (e.g. NaOH), which racemate can then be recycled for use in a process according to the present invention substantially as hereinbefore described.

Substantially as hereinbefore described an aim of a process according to the present invention is to obviate racemisation associated with prior art processes so as to yield an enantiomerically pure form of (+)duloxetine. According to the present invention this can be achieved by the resolution of (±)duloxetine as a final process step in the preparation of (+)duloxetine substantially as hereinbefore described. The present invention also solves the problem of prior art racemisation by employing the following intermediate process step in the preparation of (+)duloxetine and which represents a further preferred aspect of the present invention. More particularly, an intermediate process step employed in a process according to the present invention comprises reacting intermediate compounds of formulae (I) and (II) so as to yield a compound of formula (III), or an acid addition salt thereof:




(I)

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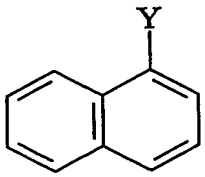
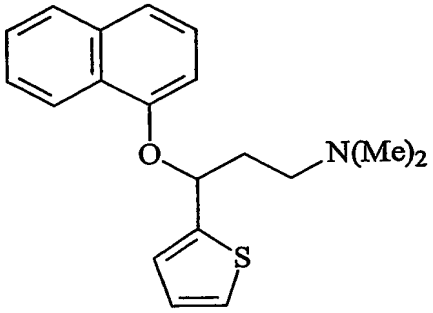



(II)




(III)

in the presence of a base and a phase transfer catalyst, where one of X and Y is hydroxy and the other is a leaving group.

Preferably the base employed can be an alkali metal hydroxide, an alkali metal carbonate, an alkali metal bicarbonate or the like. Suitably the base can be selected from the group consisting of potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate and the like. Potassium hydroxide can often be preferred.

Suitable phase transfer catalysts can be crown ethers, quaternary ammonium salts, quaternary phosphonium salts and the like. A preferred phase transfer catalyst can suitably be tetrabutyl ammonium bromide or 18-Crown-6.

A suitable leaving group as represented by X or Y can be p-toluenesulfonyl, methanesulfonyl, triphenylphosphine oxide, halo and the like, with halo being preferred.

Preferably X is hydroxy and Y is a leaving group such as halo, typically fluoro.

An intermediate of formula (III), or an acid addition salt thereof, is typically converted to (±)duloxetine by demethylating, typically in the presence of a reagent such a phenyl chloroformate or trichloroethyl chloroformate or the like to provide the corresponding intermediate, which is then hydrolysed to provide (±)duloxetine.

A further preferred process according to the present invention comprises reacting intermediate compounds of formulae (I) and (II) to yield an intermediate compound of formula (III), or an acid addition salt thereof, demethylating a compound of formula (III), or an acid addition salt, so as to yield (±)duloxetine and converting (±)duloxetine to (+)duloxetine, or an acid addition salt thereof, employing a process according to the present invention substantially as hereinbefore described.

A particularly preferred process according to the present invention comprises reacting intermediate compounds of formulae (I) and (II) where X is hydroxy and Y is fluoro, followed by oxalic acid to yield an oxalate salt of intermediate compound of formula (III), demethylating the intermediate compound of formula (III) so as to yield (±)duloxetine and converting (±)duloxetine to (+)duloxetine employing a process according to the present invention substantially as hereinbefore described. In particular it is especially preferred that resolution to yield (+)duloxetine comprises:

(i) resolving racemic (±)duloxetine with (-)di-p-toluyl tartaric acid so as to obtain (+)duloxetine di-p-toluyl tartrate, substantially free of (-)duloxetine; and

(ii) converting (+)duloxetine di-p-toluyl tartrate prepared in step (i) to (+)duloxetine hydrochloride.

The compounds employed as starting materials in the processes of the present invention can be prepared by standard procedures known in the art.

The present invention further provides (+)duloxetine, or an acid addition salt thereof, obtained by a process substantially as hereinbefore described. Such (+)duloxetine, or an acid addition salt thereof, according to the present invention can suitably be formulated to provide a pharmaceutical composition according to the present invention, and there is further provided by the present invention a pharmaceutical composition comprising (+)duloxetine, or an acid addition salt thereof, obtained by a process substantially as hereinbefore described.

The present invention will now be illustrated by the following Examples, which do not limit the scope of the invention in any way.

Example 1

N,N-dimethyl-?-(1-naphthalenyloxy)-2-thiophenepropanamine oxalate

2-(1-N,N-dimethyl-3-hydroxy)propyl amino)-thiophene (12.4gms) was dissolved in DMSO (70ml). Potassium hydroxide (18.7gms) and tetrabutyl ammonium bromide were added (0.1gms). The reaction mixture was stirred at 60°C for 1 hour and 4-fluoro naphthalene (11.7gms) was added slowly over 2 hours. After the reaction was complete, it was quenched in ice-water and extracted into toluene. The toluene layer was dried and concentrated under vacuum. The residue was dissolved in 100ml of ethyl acetate and oxalic acid (7gms) was added. The reaction mixture was stirred for 1 hour and filtered (15.5gms, 76% yield).

Example 2

(±)-N-methyl-?-(1-naphthalenyloxy)-2-thiophenepropanamine ((±) Duloxetine)

N,N-dimethyl-?-(1-naphthalenyloxy)-2-thiophenepropanamine (50gms) was dissolved in toluene (250ml). To the reaction mixture was added diisopropyl ethyl amine (24.8gms) and phenyl chloroformate (30gms) was added slowly. The reaction mixture was heated to 60°C and stirred for 2 hours. After completion of the reaction, the mixture was quenched in 50ml

of 5% sodium bicarbonate solution. The toluene layer was separated, dried and concentrated to give a residue.

The residue was dissolved in a mixture of DMSO and water. To this was added sodium hydroxide (22gms) and the reaction mixture refluxed for 8 hours. The reaction was then diluted with 700ml of water and extracted with ethyl acetate. The ethyl acetate layer was dried and concentrated to give the title compound (74%).

Example 3

(+)-N-methyl-?-(1-naphthalenyloxy)-2-thiophenepropanamine ((+) Duloxetine)

(±) Duloxetine (20gms) was dissolved in methanol (20ml) and (-)di-p-toluyl tartaric acid (6.5gms) was added. The reaction was stirred under reflux for 1 hour, methanol concentrated under vacuum, acetone (150ml) charged and cooled to 5°C. The solids obtained were filtered and dried under vacuum at 40°C to give the (-)di-p-toluyl tartrate salt of (+) duloxetine (12.5 g).

The above tartrate salt was suspended in a mixture of water and toluene and 500mg of sodium hydroxide was added under stirring. The toluene layer was separated, dried and concentrated under vacuum to residue. Ethyl acetate (20ml) was added to the residue followed by oxalic acid (2.2gms). The reaction was cooled to 5°C and the mixture stirred for 1 hour. The solids were filtered and dried under vacuum at 40°C to yield the title compound as an oxalate (6.5gms).

The methanolic mother liquor obtained after filtration of the (-)DPTA salt of (+)duloxetine was basified to pH 10 by lye solution (50% NaOH) and heated to reflux for 10 hours. Extractions with dichloromethane (100 ml) followed by concentration of the solvent yielded the racemate base (8.5 gm) having enantiomeric ratio (+/-) of 48:52 by chiral HPLC.

CLAIMS:

1. A process for preparing (+)duloxetine, or an acid addition salt thereof, which process comprises:

(i) resolving racemic (±)duloxetine with a chiral acid so as to obtain a salt of the chiral acid and (+)duloxetine, substantially free of (-)duloxetine; and

(ii) if desired, converting the salt prepared in step (i) to the free base or a further acid addition salt.

2. A process according to claim 1, wherein the chiral acid is selected from the group consisting of mandelic acid, tartaric acid, di-p-toluyl tartaric acid, dibenzoyl tartaric acid and camphor sulfonic acid.

3. A process according to claim 2, wherein the chiral acid is di-p-toluyl tartaric acid.

4. A process according to any of claims 1 to 3, wherein step (ii) comprises reacting a salt prepared in (i) with hydrochloric acid to yield (+)duloxetine hydrochloride.

5. A process for preparing (+)duloxetine hydrochloride, which process comprises:

(i) resolving racemic (±)duloxetine with di-p-toluyl tartaric acid so as to obtain (+)duloxetine di-p-toluyl tartrate, substantially free of (-)duloxetine; and

(ii) converting (+)duloxetine di-p-toluyl tartrate prepared in step (i) to (+)duloxetine hydrochloride.

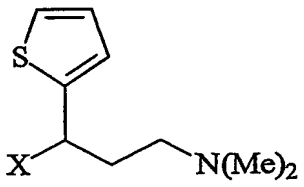
6. A process which comprises:

(i) resolving racemic (±)duloxetine with a chiral acid in a process according to any of claims 1 to 5, and obtaining a mother liquor enriched in (-)duloxetine;

(ii) converting (-)duloxetine obtained from step (i) to (±)duloxetine; and

(iii) if desired, employing (±)duloxetine obtained from step (ii) in a process according to any of claims 1 to 5.

7. A process for making (+)duloxetine or an acid addition salt thereof, comprising reacting intermediate compounds of formulae (I) and (II) so as to yield a compound of formula (III), or an acid addition salt thereof:




(I)

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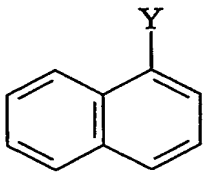
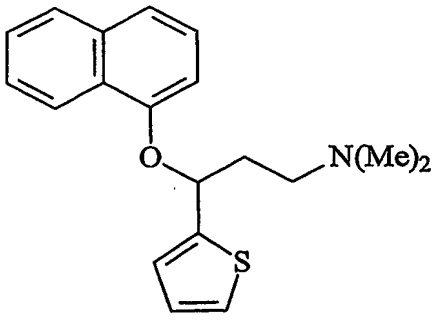



(II)



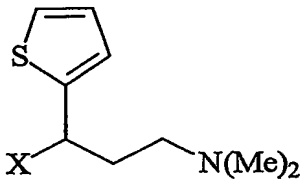

(III)

in the presence of a base and a phase transfer catalyst, where one of X and Y is hydroxy and the other is a leaving group, and subjecting a compound of formula (III), or an acid addition salt thereof, to further process steps so as to yield (+) duloxetine, or an acid addition salt thereof, substantially free of (-)duloxetine.

8. A process according to claim 7, wherein an intermediate of formula (III), or an acid addition salt thereof, is converted to (±)duloxetine by demethylating.

9. A process for making (+)duloxetine or an acid addition salt thereof, which comprises:

(i) reacting intermediate compounds of formulae (I) and (II) to yield an intermediate compound of formula (III), or an acid addition salt thereof,

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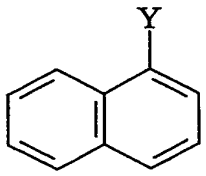


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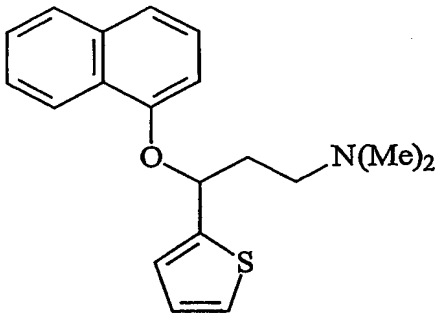



(III)

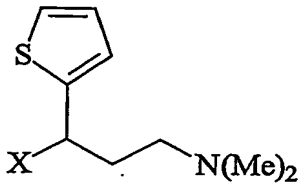
in the presence of a base and a phase transfer catalyst;

(ii) demethylating a compound of formula (III), or an acid addition salt, so as to yield (±)duloxetine; and

(iii) converting (±)duloxetine obtained in step (ii) to (+)duloxetine, or an acid addition salt thereof, employing a process according to any of claims 1 to 5.

10. A process for making (+)duloxetine hydrochloride which comprises:

(i) reacting intermediate compounds of formulae (I) and (II), where X is hydroxy and Y is fluoro, followed by oxalic acid to yield an oxalate salt of intermediate compound of formula (III)

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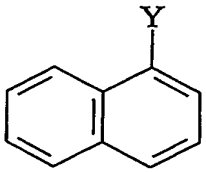


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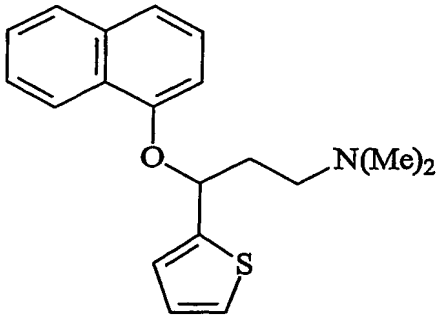



(III)

in the presence of a base and a phase transfer catalyst;

(ii) demethylating said intermediate compound of formula (III) obtained by step (i) so as to yield (±)duloxetine; and

(iii) converting (±)duloxetine obtained in step (ii) to (+)duloxetine by resolving racemic (±)duloxetine with di-p-toluyl tartaric acid so as to obtain (+)duloxetine di-p-toluyl tartrate, substantially free of (-)duloxetine, and converting said (+)duloxetine di-p-toluyl tartrate to (+)duloxetine hydrochloride.

11. A process according to any of claims 7 to 10, wherein the base is selected from the group consisting of an alkali metal hydroxide, an alkali metal carbonate and an alkali metal bicarbonate.

12. A process according to claim 11, wherein the base is selected from the group consisting of potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate and sodium bicarbonate.

13. A process according to any of claims 7 to 12, where the phase transfer catalyst is selected form the group consisting of crown ethers, quaternary ammonium salts and phosphonium salts.

14. A process according to claim 7 or 8, wherein X is hydroxy and Y is a leaving group.

15. A process according to claim 7 or 8, wherein the leaving group is halo.

16. A process according to claim 15, wherein the leaving group is fluoro.

17. A salt of a chiral acid and (+)duloxetine, substantially free of (-)duloxetine.

18. A salt of a chiral acid and (+)duloxetine, substantially free of (-)duloxetine, selected from the group consisting of (+)duloxetine mandelate, (+)duloxetine tartrate, (+)duloxetine di-p-toluyl tartrate, (+)duloxetine dibenzoyl tartrate and (+)duloxetine camphor sulfonate.

19. (+)duloxetine di-p-toluyl tartrate, substantially free of (-)duloxetine.

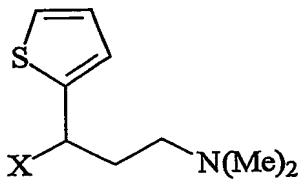
20. (+)duloxetine, or an acid addition salt thereof, obtained by a process according to any of claims 1 to 16.

21. A pharmaceutical composition comprising (+)duloxetine, or an acid addition salt thereof, obtained by a process according to any of claims 1 to 16.

## ABSTRACT

## A PROCESS FOR PREPARING DULOXETINE AND INTERMEDIATES FOR USE THEREIN

A process for preparing (+)duloxetine, or an acid addition salt thereof, which process comprises resolving racemic (±)duloxetine with a chiral acid so as to obtain a salt of the chiral acid and (+)duloxetine, substantially free of (-)duloxetine; and (ii) if desired, converting the salt prepared in step (i) to the free base or another acid addition salt as appropriate. The process can also comprise reacting intermediate compounds of formulae (I) and (II) so as to yield a compound of formula (III), or an acid addition salt thereof:

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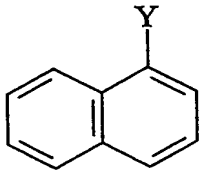


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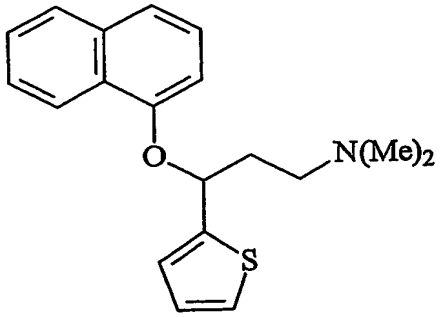


(III)

in the presence of a base and a phase transfer catalyst, where one of X and Y is hydroxy and the other is a leaving group.